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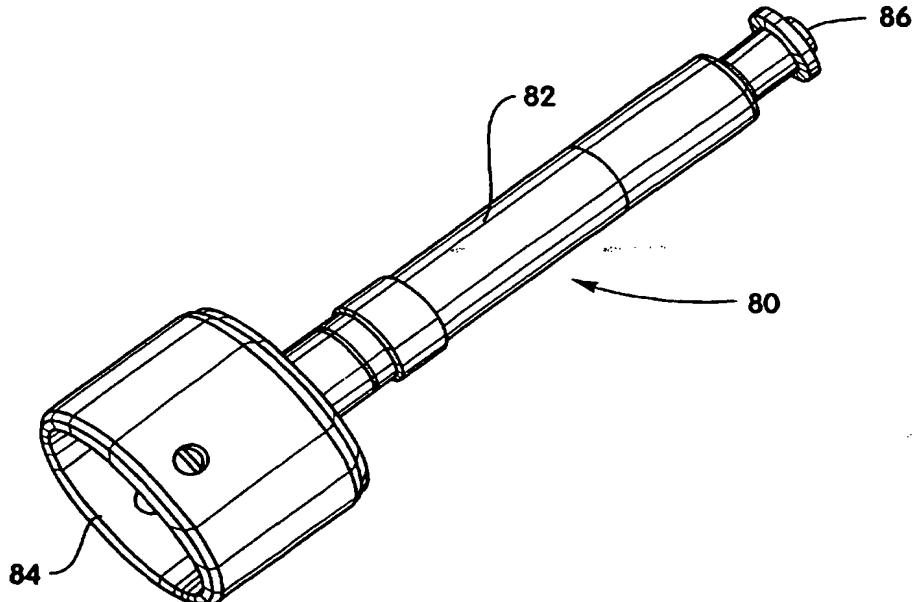
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(54) Title: APPARATUS AND METHOD FOR PIERCING SKIN WITH MICROPROTRUSIONS



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(57) Abstract: A method and device are described for applying a microprotrusion member (44) including a plurality of microprotrusions (90) to the stratum corneum with impact. The method and device are used to improve transport of an agent across the skin for agent delivery or sampling. The applicator (10, 60, 80) causes the microprotrusion member (44) to impact the stratum corneum with a certain amount of impact determined to effectively pierce the skin with the microprotrusions (90). The preferred applicator (10, 60, 80) impacts the stratum corneum with the microprotrusion member (44) with an impact of at least 0.05 joules per cm<sup>2</sup> of the microprotrusion member (44) in 10 msec or less.



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# APPARATUS AND METHOD FOR PIERCING SKIN WITH MICROPROTRUSIONS

## TECHNICAL FIELD

5 [0001] The invention relates to an apparatus and method for applying a penetrating member to the stratum corneum by impact, and more particularly, the invention relates to the use of an applicator device providing an impact to reproducibly penetrate the stratum corneum with a microprotrusion array for delivery or sampling of an agent.

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## BACKGROUND ART

15 [0002] Interest in the percutaneous or transdermal delivery of peptides and proteins to the human body continues to grow as the number of medically useful peptides and proteins becoming increasingly available in large quantities and pure form. The transdermal delivery of peptides and proteins still faces significant problems. In many instances, the rate of delivery or flux of polypeptides through the skin is insufficient, due to their large size and molecular weight, to produce a desired therapeutic effect. In addition, polypeptides and proteins are easily degraded during and after penetration 20 into the skin and prior to reaching target cells. Likewise, the passive transdermal flux of many low molecular weight compounds is too low to be therapeutically effective.

25 [0003] One method of increasing the transdermal delivery of agents relies on utilizing a skin permeation enhancer, either by pretreatment of the skin or co-delivering it with the beneficial agent. A permeation enhancer substance, when applied to a body surface through which the agent is delivered, enhances the transdermal flux of the agent. These enhancers work may function increasing the permselectivity and/or permeability of the body surface, and/or reducing the degradation of the agent.

30 [0004] Another method of increasing the agent flux involves the application of an electric current across the body surface referred to as "electrotransport." "Electrotransport" refers generally to the passage of a beneficial agent, e.g., a drug or drug precursor, through a body surface, such as skin, mucous

membranes, nails, and the like. The transport of the agent is induced or enhanced by the application of an electrical potential, which results in the flow of electric current, which delivers or enhances delivery of the agent.

Electrotransport delivery generally increases agent delivery and reduces 5 polypeptide degradation during transdermal delivery.

[0005] There also have been many attempts to mechanically penetrate or disrupt the skin in order to enhance the transdermal flux, such as, U.S. Patent Nos. 5,879,326 issued to Godshall, et al., 3,814,097 issued to Ganderton, et al., 5,279,544 issued to Gross, et al., 5,250,023 issued to Lee, et al., 10 3,964,482 issued to Gerstel, et al., Reissue 25,637 issued to Kravitz, et al., and PCT Publication Nos. WO 96/37155, WO 96/37256, WO 96/17648, WO 97/03718, WO 98/11937, WO 98/00193, WO 97/48440, WO 97/48441, WO 97/48442, WO 98/00193, WO 99/64580, WO 98/28037, WO 98/29298, and WO 98/29365. These devices use piercing elements of various shapes and 15 sizes to pierce the outermost layer (i.e., the stratum corneum) of the skin. The penetrating elements disclosed in these references generally extend perpendicularly from a thin, flat member, such as a pad or sheet. The penetrating elements, often referred to as microblades, are extremely small in some devices. Some of these microblades have dimensions (i.e., a 20 microblade length and width) of only about 25 - 400  $\mu\text{m}$  and a microblade thickness of only about 5 - 50  $\mu\text{m}$ . Other penetrating elements are hollow needles having diameters of about 10  $\mu\text{m}$  or less and lengths of about 50-100  $\mu\text{m}$ . These tiny stratum corneum piercing/cutting elements are meant to make correspondingly small microslits/microcuts in the stratum corneum for 25 enhanced transdermal agent delivery, or for enhanced transdermal efflux of a body analyte, therethrough. The perforated skin provides improved flux for sustained agent delivery or sampling through the skin. In many instances, the microslits/microcuts in the stratum corneum have a length of less than 150  $\mu\text{m}$  and a width which is substantially smaller than their length. 30 [0006] When microprotrusion arrays are used to improve delivery or sampling of agents through the skin, consistent, complete, and repeatable penetration of the skin by the microprotrusions is desired. Manual application of a skin patch including microprotrusions often results in significant variation

in puncture depth across the microprotrusion array. In addition, manual application results in large variations in puncture depth between applications due to the manner in which the user applies the array. Accordingly, it would be desirable to be able to apply a microprotrusion array to the stratum corneum with an automatic or semi-automatic device which provides microprotrusion skin penetration in a consistent and repeatable manner.

5 [0007] It would be desirable to provide an applicator for consistent and repeatable application of a microprotrusion array to the skin with the applicator applying an impact capable of achieving effective penetration of the stratum corneum with the microprotrusion array.

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### DISCLOSURE OF THE INVENTION

[0008] The present invention relates to a method and device for applying a microprotrusion member including a plurality of microprotrusions to the stratum corneum with impact. Piercing the skin with the microprotrusions is used to improve transport of an agent across the skin. The applicator causes the microprotrusion member to impact the stratum corneum with a certain amount of impact determined to effectively pierce the skin with the microprotrusions. The preferred applicator impacts the stratum corneum with the microprotrusion member with an impact of at least 0.05 joules per  $\text{cm}^2$  of the microprotrusion member in 10 msec or less.

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[0009] In accordance with one aspect of the present invention, a method is disclosed for forming a plurality of microslits through the stratum corneum through which an agent can be delivered or sampled. The method involves providing a microprotrusion member having a plurality of stratum corneum-piercing microprotrusions, and causing the microprotrusions to impact the stratum corneum with an impact of at least 0.05 joules per  $\text{cm}^2$  of the microprotrusion member in 10 msec or less.

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[00010] In accordance with another aspect of the present invention, a device is disclosed for forming a plurality of microslits through the stratum corneum through which an agent can be delivered or sampled. The device includes an applicator having a stratum corneum contacting surface, and a microprotrusion member having a plurality of stratum corneum-piercing

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microprotrusions, the microprotrusion member mounted on the applicator, wherein the applicator, once activated, causes the microprotrusion member to impact the stratum corneum under conditions of at least 0.05 joules per  $\text{cm}^2$  of microprotrusion member in 10 msec or less.

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### BRIEF DESCRIPTION OF THE DRAWINGS

[00011] The invention will now be described in greater detail with reference to the preferred embodiments illustrated in the accompanying drawings, in which like elements bear like reference numerals, and wherein:

10 FIG. 1 is a side cross sectional view of an applicator device in an initial configuration prior to cocking;

FIG. 2 is a side cross sectional view of the applicator device of FIG. 1 in a cocked position with a patch retainer attached to the applicator;

15 FIG. 3 is a side cross sectional view of the applicator device of FIG. 1 with the patch retainer of FIG. 2 after the piston has been released to apply the patch;

FIG. 4 is a perspective view of an alternative embodiment of an applicator device;

20 FIG. 5 is a perspective view of a portion of one example of a microprotrusion array;

FIG. 6 is a side sectional view of a pressure driven applicator device; and

25 FIG. 7 is a graph of dose M (in  $\mu\text{g}$ ) of ovalbumin delivered over two time periods (5 seconds and 1 hour) from dry coated microprotrusions arrays applied using manual finger pressure (non-hatched bars) and using automatic applicators in accordance with the present invention (hatched bars).

### MODES FOR CARRYING OUT THE INVENTION

[00012] FIG. 1 illustrates an applicator device 10 for repeatable impact application of an array of microprotrusions to the stratum corneum. The applicator device 10 is configured to achieve a predefined and consistent impact of a microprotrusion member including an array of microprotrusions on the stratum corneum to provide acceptable penetration of the stratum

corneum with the microprotrusions. In particular, the applicator device 10 has been designed to optimize the power per unit area of the impact to achieve effective penetration of the stratum corneum with the microprotrusions.

[00013] As will be described in further detail below, it has been determined 5 that the applicator device 10 should deliver range of power per unit area of a microprotrusion member for effective penetration of the stratum corneum. The range of power per unit area is represented as a minimum energy per unit area delivered to the skin site in a maximum amount of time.

[00014] One embodiment of the applicator device 10, as shown in FIGS. 1-10, includes a device body 12 and a piston 14 movable within the device body. A cap 16 is provided on the device body 12 for activating the applicator to impact the stratum corneum with a microprotrusion member (not shown in FIG. 1). An impact spring 20 is positioned around a post 22 of the piston 14 and biases the piston downward with respect to the device body 12. The 15 piston 14 has a lower surface 18 which is substantially planar or configured to a bodily surface. Upon activation of the applicator device the impact spring 20 moves the piston 14 and causes a microprotrusion member, such as a transdermal patch containing a microprotrusion array to impact and pierce the stratum corneum.

20 [00015] FIG. 1 shows the piston 14 in an uncocked position, while FIG. 2 shows the piston in the cocked position. When the applicator device is cocked, the piston 14 is pressed up inside the device body 12 and locked in place by a locking mechanism. The locking mechanism includes a catch 26 on the post 22 and a flexible finger 28 on the device body 12 having a 25 corresponding latch 30. As the piston 14 is moved toward the device body 12, compressing the impact spring 20, the catch 26 flexes the finger 28 and snaps over the corresponding latch 30 of the flexible finger. The cocking step may be performed by a single compression motion which both cocks and locks the piston 14 in the cocked position.

30 [00016] FIG. 2 illustrates the applicator device 10 with the piston 14 in a cocked configuration. As shown in FIG. 2, with the device in the cocked position, the catch 26 and latch 30 on the piston 14 and device body 12 are

releasably engaged preventing downward motion of the piston in the device body.

[00017] FIG. 2 also illustrates a retainer ring 34 mounted on the device body 12. The retainer ring 34 has a first end 40 which is configured to friction fit onto the device body 12. A second end 42 of the retainer ring 34 provides a stratum corneum contacting surface. A microprotrusion member 44 including the microprotrusions is mounted between the first and second ends 40, 42 of the retainer ring 34. The microprotrusion member 44 is suspended in the retainer ring 34. The manner in which the microprotrusion member 44 is mounted in the retainer ring 34 and the location of the microprotrusion member may vary. For example, the microprotrusion member 44 may be positioned adjacent the second end 42 of the retainer ring 34.

[00018] According to one example, the microprotrusion member 44 is connected by frangible sections of base material to an annular ring of base material which is adhered to the retainer ring 34. When the piston 14 of applicator device 10 is released, the microprotrusion member 44 is separated from the retainer ring 34 by the downward force of the piston 14. Alternatively, the microprotrusion member 44 may be releasably attached to the piston 14 or positioned on the skin beneath the piston.

[00019] The retainer ring 34 is attached to the device body 12 after cocking of the piston 14. The retainer ring 34 is attached by a snap in connection, a bayonet fitting, or a slide on fitting which allows the retainer ring 34 to slide on the device body 12 in a direction normal to the axis of the applicator.

[00020] The applicator device 10 has been described for use with a microprotrusion member 44, such as a transdermal patch. A transdermal patch useful with the present invention generally includes a microprotrusion array, an agent reservoir, and a backing. However, the applicator device 10 may also be used with a microprotrusion member without an agent reservoir. In this case, the microprotrusion member is used as a pretreatment which is followed by the application or sampling of an agent with a separate device. Alternatively, the microprotrusion member may incorporate the agent as a coating on the microprotrusions, e.g. for delivering a vaccine intradermally.

[00021] The activation of the applicator device 10 by releasing the locking mechanism is performed by downward force applied to the applicator cap 16 while the second end 42 of the retainer ring 34 is held against the skin with a hold down force. The cap 16 is biased upwards by a hold down spring 24 which is positioned between the device body 12 and the cap. The cap 16 includes a pin 46 extending downward from the cap. When the cap 16 is pressed downward against the bias of the hold down spring 24, the pin 46 contacts a ramp 48 on the flexible finger 28 moving the flexible finger outward and disengaging the latch 30 of the flexible finger from the catch 26. When the predetermined hold down force is achieved, the piston 14 is released and moves downward impacting the stratum corneum with the microprotrusion member 44. FIG. 3 illustrates the applicator device 10 after the device has been activated and a microprotrusion member has been impacted against the stratum corneum.

[00022] The hold down spring 24 is selected such that a predetermined hold down force must be achieved before the applicator device 10 is activated. The hold down force causes the stratum corneum to be stretched by the surface 42 of the retainer ring 34 so that the skin is under optimal tension at the time the microprotrusion member 44 impacts the skin.

[00023] The hold down force applied by the hold down spring 24 is preferably selected to cause the second end 42 of the retainer right 34 to apply a tension to the skin in the range of about 0.01 to 10 megapascals (MPa), more preferably about 0.05 to 2 MPa. The hold down force with which the skin contacting surface 42 of the retainer ring 34 is held against the skin when the piston 14 is released, is preferably at least 0.5 kg, and more preferably, at least 1.0 kg.

[00024] A balance between the hold down spring 24 and the impact spring 20 allows the cocking of the piston 14 by pressing on the cap 16 without causing the finger 46 to release the locking mechanism. In other words, upon application of a cocking force to the applicator device 10, the impact spring 20 will be deflected prior to the deflection of the hold down spring 24.

[00025] The impact spring 20 is selected to apply a force to the piston which achieves a predetermined impact of the microprotrusion member 44 against

the stratum corneum. The microprotrusion member 44 is impacted with an energy which provides a desired skin penetration with the microprotrusions. The impact spring 20 is also preferably selected to achieve the desired skin penetration without exceeding an impact which causes discomfort to the 5 patient.

[00026] The impact of the microprotrusion member against the stratum corneum is determined by the following features of the applicator device: 1) the distance (x) the piston 14 travels from the cocked and locked position (shown in FIG. 2) to the skin; 2) the amount of compression in the impact 10 spring 20 when the piston 14 is in the cocked and locked position; 3) the rate (k) of the impact spring 20 as it moves from the cocked and locked position to the skin impacting position; 4) the time (t) in which the potential energy (PE) of the impact spring 20 is imparted as kinetic energy (KE) to the skin; 5) the mass (m) of the moving impact piston and patch with the microprotrusion 15 array; 6) any energy loss (L) associate with friction or breakage of the frangible connections holding the patch on the retainer; and 7) the area (A) of impact. The impact is also effected by conditions external to the applicator device including the configuration of the microprotrusion member and the condition of the skin (e.g., stretched or unstretched) on impact. These 20 conditions external to the applicator device have been taken into account in determining the desired impact power.

[00027] The power of impact (P) per unit area (A) of the microprotrusion array is defined as follows:

$$P/A = (KE) / (A)(t)$$

25 wherein:  $PE = KE + L$

$$PE = 0.5(k)(x)^2$$

$$KE = 0.5(m)(v)^2$$

$$P = (KE) / (t)$$

$$P/A = (KE) / (A)(t)$$

### 30 EXAMPLES

[00028] The following are examples of applicator systems having impact springs which provide acceptable power per unit area for delivery of a microprotrusion member, as tested on human skin. The applicator 10

described earlier herein was configured with three different impact springs having different spring constants and lengths as shown below. These three applicator/spring configurations were found to be acceptable for delivery of microblade arrays having the three different areas listed below. The 5 microprotrusion device delivered was substantially similar to the device illustrated in FIG. 5 having microblades with lengths of about 250  $\mu\text{m}$ .

Microblade array area	Spring	spring constant (K)	spring length (L)	Total Energy Delivered	Energy/Area
1 $\text{cm}^2$	#71512	9.3 lb/in	1.75 in	0.36 J	0.36 J/ $\text{cm}^2$
2 $\text{cm}^2$	#71526	14 lb/in	1.75 in	0.63 J	0.32 J/ $\text{cm}^2$
3.3 $\text{cm}^2$	#71527	12 lb/in	2.00 in	1.07 J	0.32 J/ $\text{cm}^2$

[00029] The impact spring 20 is preferably selected to deliver a minimum 10 amount of energy of 0.05 Joules per  $\text{cm}^2$ , which is delivered in less than 10 milliseconds (msec). A preferred amount of energy is a minimum of 0.10 Joules per  $\text{cm}^2$ , which is delivered in less than 1 msec. A maximum amount of energy delivered by the impact spring 20 is about 0.3 Joules per  $\text{cm}^2$ . The maximum amount of energy delivered has been determined based on the 15 balance between the use of additional energy to achieve additional blade penetration and a desire to prevent discomfort (e.g. pain and bruising) caused by impacting the stratum corneum with the microprotrusion member.

[00030] FIG. 4 illustrates an alternative embodiment of an applicator 80 having a different shape and a release button 86 for manual activation. 20 According to this embodiment, a user grasps a handle 82 of the applicator device 80 and presses a lower end 84 of the device against the stratum corneum. Activation of the applicator device 80 is performed manually by pressing the release button 86 and the amount of hold down force is controlled manually and independently of the when the release button 86 is 25 pressed. The applicator 80 of FIG. 4 may include a hold down indicator on the applicator handle 82 which indicates to the user (e.g., by means of an

audible, tactile, or visible signal) when the predetermined hold down force has been achieved and the release button 86 should be pressed.

[00031] The applicator devices 10, 80 according to the present invention have been described with respect to an upright orientation in which the 5 microprotrusion member 44 is applied from a piston side of the device which is illustrated at the bottom of the devices in the figures. It should be understood that the applicator devices may be used in other orientations.

[00032] While the applicator devices 10 and 80 are spring-loaded, it will be appreciated by those skilled in the art that other known energy sources (e.g., 10 pressure, electricity, magnets and other biasing members besides compression springs such as tension/extension springs and rubber bands) can be used in place of the spring 20 and are considered equivalents thereof as long as such alternative energy source provides the prescribed minimum power at impact.

[00033] One example of a pressure driven applicator device is shown in FIG. 6. Pressure driven applicator 60 has a tubular body 61 with a recessed cap 63. The recessed cap has a central orifice 64 through which is disposed rod 67 of piston rod unit 65. At the upper end of rod 67 is disposed a piston 66 which slidably and sealingly engages the inner surface of body 61. As 20 can be seen, the piston 66 also divides the interior space within body 61 into an upper chamber 71 and a lower chamber 72. Rod 67 also slidably and sealingly engages the central orifice 64 in recessed cap 63. Disposed on the lower end of rod 67 is an impact head 68 which is adapted to impact the skin-piercing microprotrusion member described elsewhere herein against the 25 patient's skin. To operate the applicator 60, the piston 66 is moved from a position adjacent recessed cap 63 and slid upwardly towards orifice 69 by pressing on impact head 68. As piston 66 moves upwardly within the interior of body 61, air within chamber 71 is expelled through orifice 69. Further, because of the sealing contact of the piston 66 with the inside surface of body 30 61 and the sealing contact of the rod 67 with orifice 64, a partial vacuum is formed within chamber 72. When impact head 68 engages the lower surface of recessed cap 63, a sliding catch 74 is pressed through opening 73 in body 61. Optionally, a second sliding catch 74' is disposed in opening 73'. Thus,

the sliding catches 74 and 74' act to hold the impact head 68 against cap 63 against the force exerted by the partial vacuum within chamber 72.

Once secured by sliding catches 74 and 74', the microprotrusion member can be mounted on the lower surface of impact head 68. Once this is done, the 5 applicator 60 is placed against the patient's skin with edge 62 contacting the skin. The sliding catch 74 is then pulled out causing the impact head 68 to impact the mounted microprotrusion member against the skin, causing the microprotrusions to pierce the skin.

[00034] Optionally, the orifice 69 may be eliminated. In such a 10 configuration, the piston rod unit 65 is driven not only by a partial vacuum formed within chamber 72 but also a positive (i.e., above atmospheric) pressure within chamber 71.

[00035] FIG. 5 illustrates a portion of one embodiment of a microprotrusion member for piercing the stratum corneum for use with the present invention. 15 FIG. 5 shows a plurality of microprotrusions in the form of microblades 90. The microblades 90 extend at a substantially 90° angle from a sheet 92 having openings 94. The sheet 92 may be incorporated in an agent delivery patch or an agent sampling patch which includes an agent reservoir and an adhesive for adhering the patch to the stratum corneum. Examples of agent 20 delivery and sampling patches which incorporate a microprotrusion array are found in WO 97/48440, WO 97/48441, WO 97/48442. The microprotrusion array of FIG. 5 without a reservoir may also be applied alone as a skin pretreatment.

[00036] The term "microprotrusion" as used herein refers to very tiny 25 stratum corneum piercing elements typically having a length of less than 500  $\mu\text{m}$ , and preferably less than 250  $\mu\text{m}$ , which make a penetration in the stratum corneum. In order to penetrate the stratum corneum, the microprotrusions preferably have a length of at least 10  $\mu\text{m}$ , more preferably at least 50  $\mu\text{m}$ . The microprotrusions may be formed in different shapes, such as needles, 30 hollow needles, blades, pins, punches, and combinations thereof.

[00037] The term "microprotrusion member" as used herein refers to a member including a plurality of microprotrusions for piercing the stratum corneum. The microprotrusion member may be formed by cutting a plurality

of blades from a thin sheet and folding each of the blades out of the plane of the sheet to form the configuration shown in FIG. 5. The microprotrusion member may also be formed in other known manners, such as by connecting multiple strips having microprotrusions along an edge of each of the strips as disclosed in Zuck WO 99/29364 which is incorporated herein by reference. The microprotrusion member may include hollow needles which inject a liquid formulation.

[00038] Examples of microprotrusion arrays are described in U.S. Patent Nos. 5,879,326 issued to Godshall, et al., 3,814,097 issued to Ganderton, et al., 5,279,544 issued to Gross, et al., 5,250,023 issued to Lee, et al., 3,964,482 issued to Gerstel, et al., Reissue 25,637 issued to Kravitz, et al., and PCT Publication Nos. WO 96/37155, WO 96/37256, WO 96/17648, WO 97/03718, WO 98/11937, WO 98/00193, WO 97/48440, WO 97/48441, WO 97/48442, WO 98/00193, WO 99/64580, WO 98/28037, WO 98/29298, and WO 98/29365, all of which are incorporated herein by reference in their entirety.

[00039] The device of the present invention can be used in connection with agent delivery, agent sampling, or both. In particular, the device of the present invention is used in connection with transdermal drug delivery, transdermal analyte sampling, or both. Examples of agents which may be delivered include drugs and vaccines. An example of a body analyte which may be sampled is glucose. Transdermal delivery devices for use with the present invention include, but are not limited to passive devices, osmotic devices, pressure-driven devices, and electrotransport devices. Transdermal sampling devices for use with the present invention include, but are not limited to, passive devices, negative pressure driven devices, osmotic devices, and reverse electrotransport devices. The transdermal devices of the present invention may be used in combination with other methods of increasing agent flux, such as skin permeation enhancers.

[00040] The device of the present invention may be used with a microprotrusion member, such as a transdermal delivery or sampling patch having adhesive for attaching the patch to the skin. Alternatively, the microprotrusion member and a delivery or sampling patch may be two

separate elements with the microprotrusion member used for pretreatment prior to application of the delivery or sampling patch.

#### Example 1

[00041] Titanium microprotrusion embers comprising a circularsheet (sheet area was 2 cm<sup>2</sup>) having microprotrusions with the shape and configuration shown in FIG. 5 (microprotrusion length of 360 µm, and a microprotrusion density of 190 microprotrusions/cm<sup>2</sup>) were coated with the model protein vaccine ovalbumin. A 200 mg/mL aqueous coating solution of fluorescein-tagged ovalbumin was prepared. For coating, the microprotrusion members were immersed briefly in this solution, blown dry, and allowed to dry overnight at room temperature. Subsequent analysis demonstrated that the microprotrusion members were coated with ovalbumin at 200 to 250 µg/cm<sup>2</sup>.

[00042] A study was performed in hairless guinea pigs (HGP) to evaluate ovalbumin absorption into the skin after short (5 second) application of the microprotrusion members. The system applied comprised a coated microprotrusion member adhered to the center of a low density polyethylene (LDPE) backing with the acrylate adhesive (8 cm<sup>2</sup> disc). In one group of five HGP, the systems were applied with an impact applicator. The impact applicator impacted the system against the animals' skin with an impact energy of 0.42 J in less than 10 m sec and the system was removed after 5 seconds contact with the skin. In a second group of five HGP, the system was applied to the skin using a 2 kg/cm<sup>2</sup> manual pressure, held in place for 5 seconds, then removed. In both groups, penetration was similar as evidenced by good retention of the microprotrusions into the skin. Following removal of the system, residual drug was thoroughly washed from the skin and a 8 mm skin biopsy was taken at the location of the microprotrusion member application. The total amount of ovalbumin delivered into the skin was determined by dissolving the skin biopsy sample in hyamine hydroxide (diisobutylcresoxyethoxyethyl) (dimethyl) benzylammonium hydroxide, 1 M in ethanol, sold by J.T. Baker (NJ, USA) and quantitation performed by fluorimetry. Results showed that impact application resulted in an average delivery of 30.1 µg ovalbumin while only 6.6 µg of ovalbumin was delivered on average with manual application.

### Example 2

[00043] A second experiment was performed with dry-coated ovalumin to compare delivery following impact and manual application using a different titanium microprotrusion member and a longer application time. A 200 mg/mL aqueous coating solution of fluorescein-tagged ovalbumin was prepared. The microprotrusion members (micropjection length 214  $\mu\text{m}$ , no retention feature, 292 micropjections/cm<sup>2</sup>, 2 cm<sup>2</sup> disc) were immersed briefly in the coating solution, blown dry and allowed to dry overnight at room temperature. Subsequent analysis demonstrated that the microprotrusion members were coated with ovalbumin at 200 to 250  $\mu\text{g}/\text{cm}^2$ .

[00044] The delivery study was performed in hairless guinea pigs (HGP). The system applied comprised a coated microprotrusion members adhered to the center of a LDPE backing with acrylate adhesive (8 cm<sup>2</sup> disc). In one group of five HGP, microprotrusion member application was performed with an impact applicator (0.2 J/cm<sup>2</sup> in less than 10 msec) and the system was removed after 5 seconds contact with the skin. In a second group of five HGP, the system was applied to the skin using a 2 kg/cm<sup>2</sup> manual pressure, held in place for 5 seconds, then removed. Two additional groups of hairless guinea pigs were treated as described above except that, following application, the system was left in contact with the skin for 1 hour. Following removal of the system, residual drug was thoroughly washed from the skin and a 8 mm skin biopsy was taken at the location of the microprotrusion member application. The total amount of ovalbumin delivered into the skin was determined by dissolving the skin biopsy sample in hyamine hydroxide and quantitation performed by fluorimetry. The results of amount of ovalbumin delivered (M) for the two time periods (t) are presented in FIG. 7 and demonstrate that higher delivery following impact application as compared to manual application is independent of the application time.

[00045] Examples 1 and 2 demonstrate that the higher amounts of ovalbumin delivered using impact application, as compared with manual application, is independent of the microprotrusion members design, the type of coating and the application time.

[00046] While the invention has been described in detail with reference to the preferred embodiments thereof, it will be apparent to one skilled in the art that various changes and modifications can be made and equivalents employed, without departing from the present invention.

**What is claimed is:**

1. A method of delivering or sampling an agent through the stratum corneum, comprising:
  - 5 providing a microprotrusion member having one or more stratum corneum-piercing microprotrusions;
    - 10 forming one or more microslits through the stratum corneum by causing said microprotrusions to impact the stratum corneum with a power of at least 0.05 joules per  $\text{cm}^2$  of the microprotrusion member in 10 milliseconds or less; and
    - 15 delivering or sampling an agent through said microslits.
  2. The method of claim 1, wherein said agent comprises a drug.
  - 15 3. The method of claim 1, wherein said agent comprises a vaccine.
  4. The method of claim 1, wherein said agent comprises a coating on the microprotrusion member.
  - 20 5. The method of claim 1, wherein the microprotrusion member impacts the stratum corneum with a power of at least 0.1 joules per  $\text{cm}^2$  of the microprotrusion member in 10 milliseconds or less.
  - 25 6. The method of Claim 1, wherein the microprotrusion member impacts the stratum corneum with a power of at least 0.05 joules per  $\text{cm}^2$  of the microprotrusion member in 1 milliseconds or less.
  7. The method of claim 1, wherein said agent is a body analyte.
  - 30 8. The method of claim 7, wherein said body analyte is glucose.
  9. The method of claim 1, wherein the microprotrusions pierce the stratum corneum to a depth of up to about 500  $\mu\text{m}$ .

10. The method of Claim 1, wherein the microprotrusions are microblades.
11. The method of Claim 1, wherein said impact is caused by activating an impact applicator.
- 5 12. The method of Claim 11, wherein the impact applicator is activated when the applicator is held against the stratum corneum with a hold down force of at least 0.5 kg.
- 10 13. The method of Claim 12, wherein the applicator is driven by an energy source selected from the group consisting of a biasing member, pressure, electricity and magnetism.
- 15 14. The method of Claim 13, wherein the biasing member comprises a spring.
- 15 15. The method of Claim 13, wherein the pressure is selected from the group consisting of positive pressure, partial vacuum and a combination thereof.
- 20 16. A device for forming one or more microslits through the stratum corneum through which an agent can be delivered or sampled, comprising:
  - an applicator having a contacting surface; and
  - a microprotrusion member having one or more stratum corneum piercing microprotrusions, the microprotrusion member being releasably mounted on said applicator, wherein said applicator, once activated, brings said contacting surface into contact with said microprotrusion member in such a manner that said microprotrusion member strikes the stratum corneum with a power of at least 0.05 joules per  $\text{cm}^2$  of microprotrusion member in 10 milliseconds or less.
- 30 17. The device of claim 16, wherein said applicator is driven by an energy source selected from the group consisting of a biasing member, pressure, electricity and magnetism

18. The device of claim 17, wherein said biasing member comprises a spring.
19. The device of claim 18, wherein said spring is an impact spring and applies an impact having a power of at least 0.05 joules per  $\text{cm}^2$  of 5 microprotrusion member in 10 milliseconds or less.
20. The device of claim 16, wherein said microprotrusions are microblades.
21. The device of claim 16, wherein said applicator further comprises a 10 second spring for achieving a hold down force prior to activation.
22. The device of claim 21, wherein said second spring requires a hold down force of at least 0.5 kg to be applied to the applicator before the activation of the applicator.

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23. The device of claim 22, further comprising an indicator which indicates when a predetermined hold down force is applied to the applicator.
24. The device of claim 23, wherein said indicator provides an audible, tactile, 20 or visible signal to indicate when the predetermined hold down force is applied.
25. The device of claim 16, wherein said applicator causes the microprotrusion member to impact the stratum corneum with a power of at 25 least 0.1 joules per  $\text{cm}^2$  of the microprotrusion member in 10 milliseconds or less.
26. The device of claim 16, wherein said applicator is activated when the applicator is pressed against the stratum corneum with a force of at least 0.5 30 kg.
27. The device of claim 16, wherein said applicator causes the microprotrusion member to impact the stratum corneum with a power of at

least 0.05 joules per  $\text{cm}^2$  of the microprotrusion member in 1 millisecond or less.

28. The device of claim 16 wherein said microprotrusion member includes a substrate wherein said one or more microprotrusions extend from said substrate, said one or more microprotrusions having a length of less than 500  $\mu\text{m}$ .

29. The device of claim 16, further comprising an agent.

10 30. The device of claim 29 wherein said agent is a drug or a vaccine.

31. The device of claim 29, wherein said agent comprises a coating on the microprotrusion member.

15 31. The device of claim 29, wherein the agent comprises a body analyte and the device further comprises an agent reservoir for collecting said body analyte.

20 32. The device of claim 29, wherein said agent comprises a beneficial agent and said device further comprises a reservoir containing said agent therein, said reservoir being capable of being placed in agent transmitting relation with the stratum corneum.

25 33. A method of delivering or sampling an agent through the stratum corneum, comprising:

providing a microprotrusion member having one or more stratum corneum-piercing microprotrusions;

30 forming one or more microslits through the stratum corneum by causing said microprotrusions to impact the stratum corneum with a power of at least 0.05 joules per  $\text{cm}^2$  of the microprotrusion member in 10 milliseconds or less.

34. The method of claim 33 wherein the microprotrusion member impacts the stratum corneum with a power of at least 0.1 joules per  $\text{cm}^2$  of the microprotrusion member in 10 milliseconds or less.
- 5 35. The method of claim 33, wherein the microprotrusion member impacts the stratum corneum with a power of at least 0.05 joules per  $\text{cm}^2$  of the microprotrusion member in 1 millisecond or less.
- 10 36. The method of claim 33, wherein the microprotrusions pierce the stratum corneum to a depth of up to about 500  $\mu\text{m}$ .
37. The method of claim 33, wherein the microprotrusions are microblades.
- 15 38. A device for impacting a microprotrusion member, said microprotrusion member having thereon one or more microprotrusions, said microprotrusion member adapted to form one or more microslits through the stratum corneum through which an agent can be delivered or sampled, said device comprising:
  - an applicator having a contacting surface; and
  - 20 said applicator adapted to cause said contacting surface to impact said microprotrusion member in such a manner that said microprotrusion member strikes the stratum corneum with a power of at least 0.05 joules per  $\text{cm}^2$  of microprotrusion member in 10 milliseconds or less.

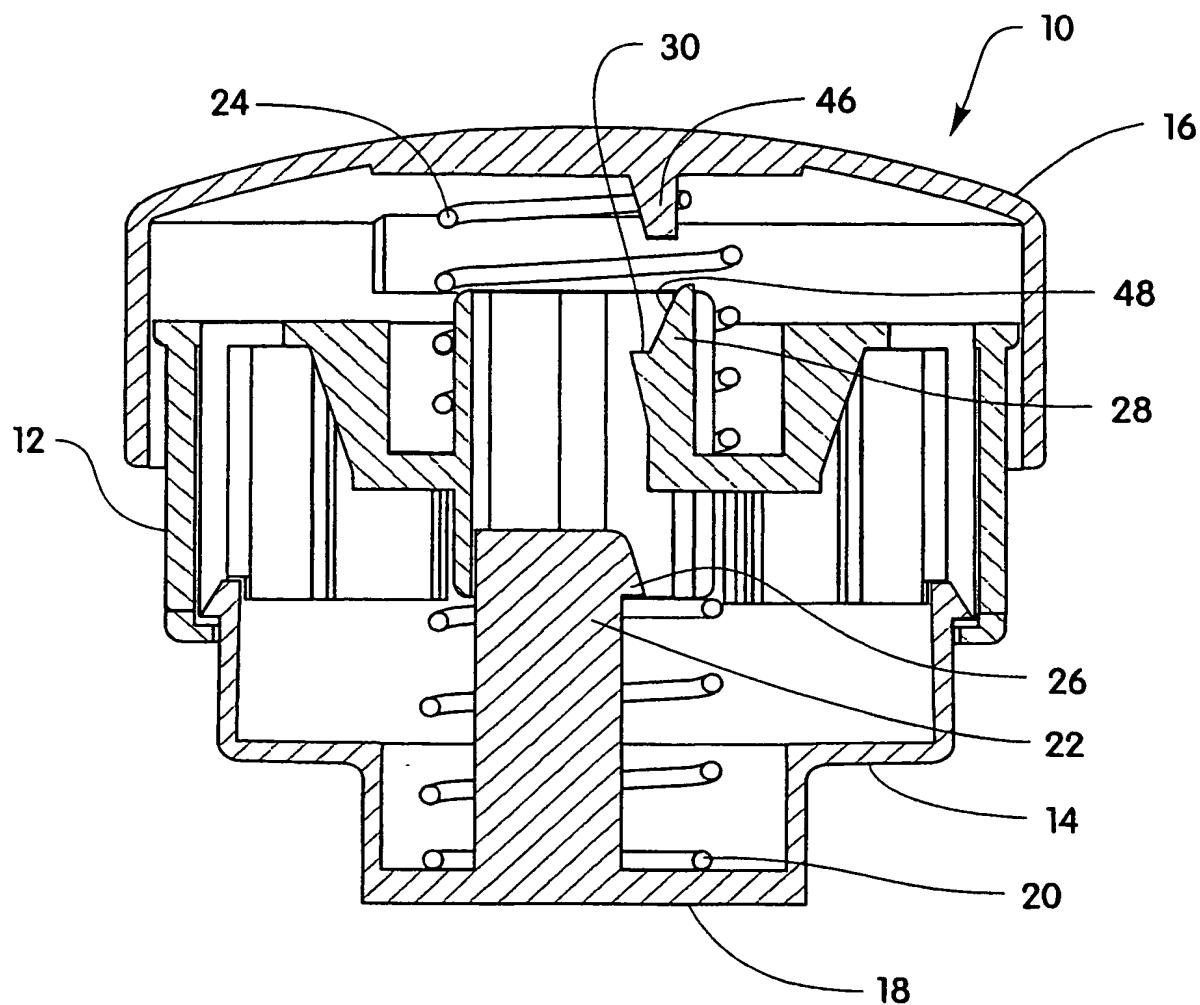


FIG. 1

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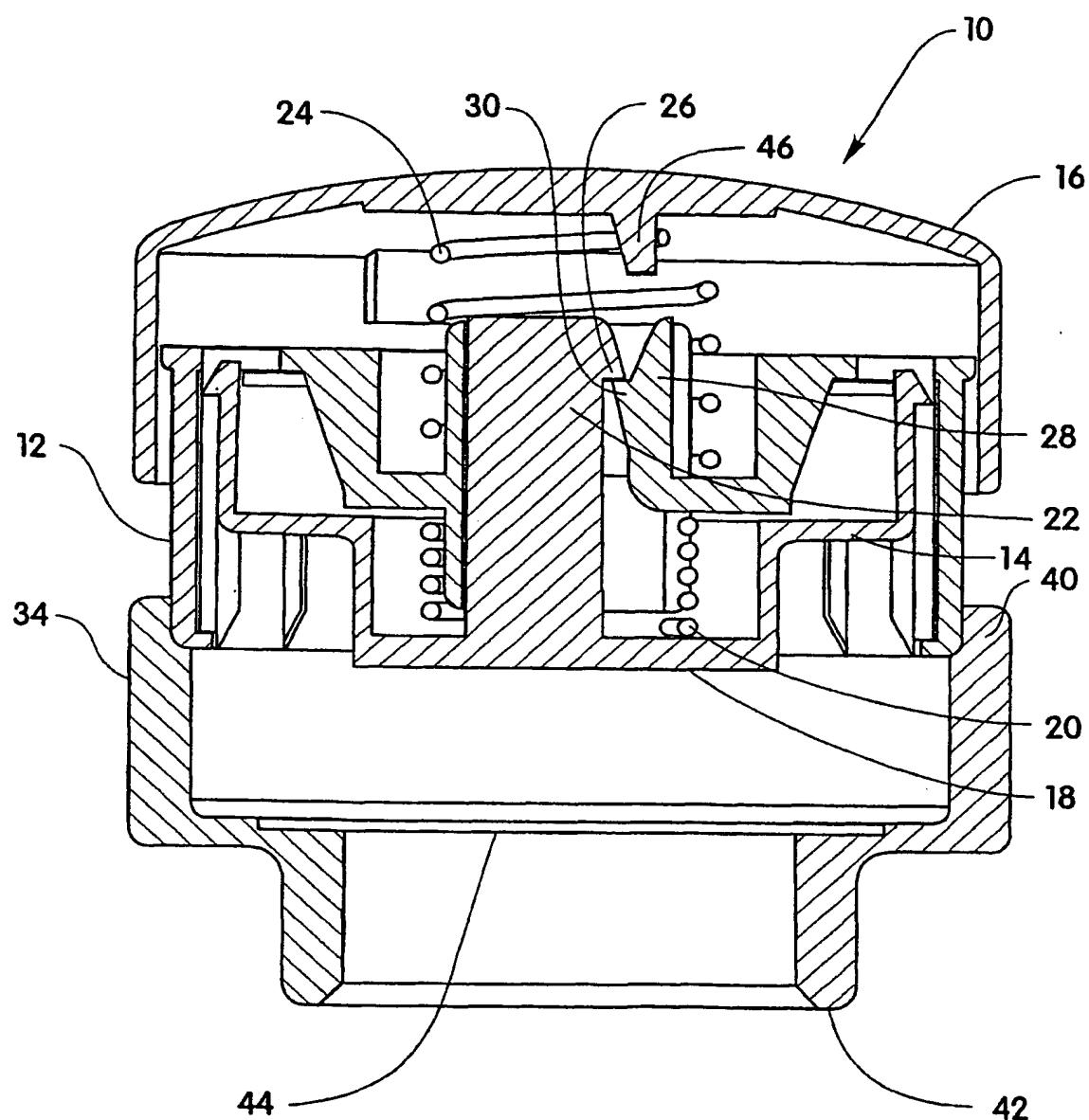


FIG. 2

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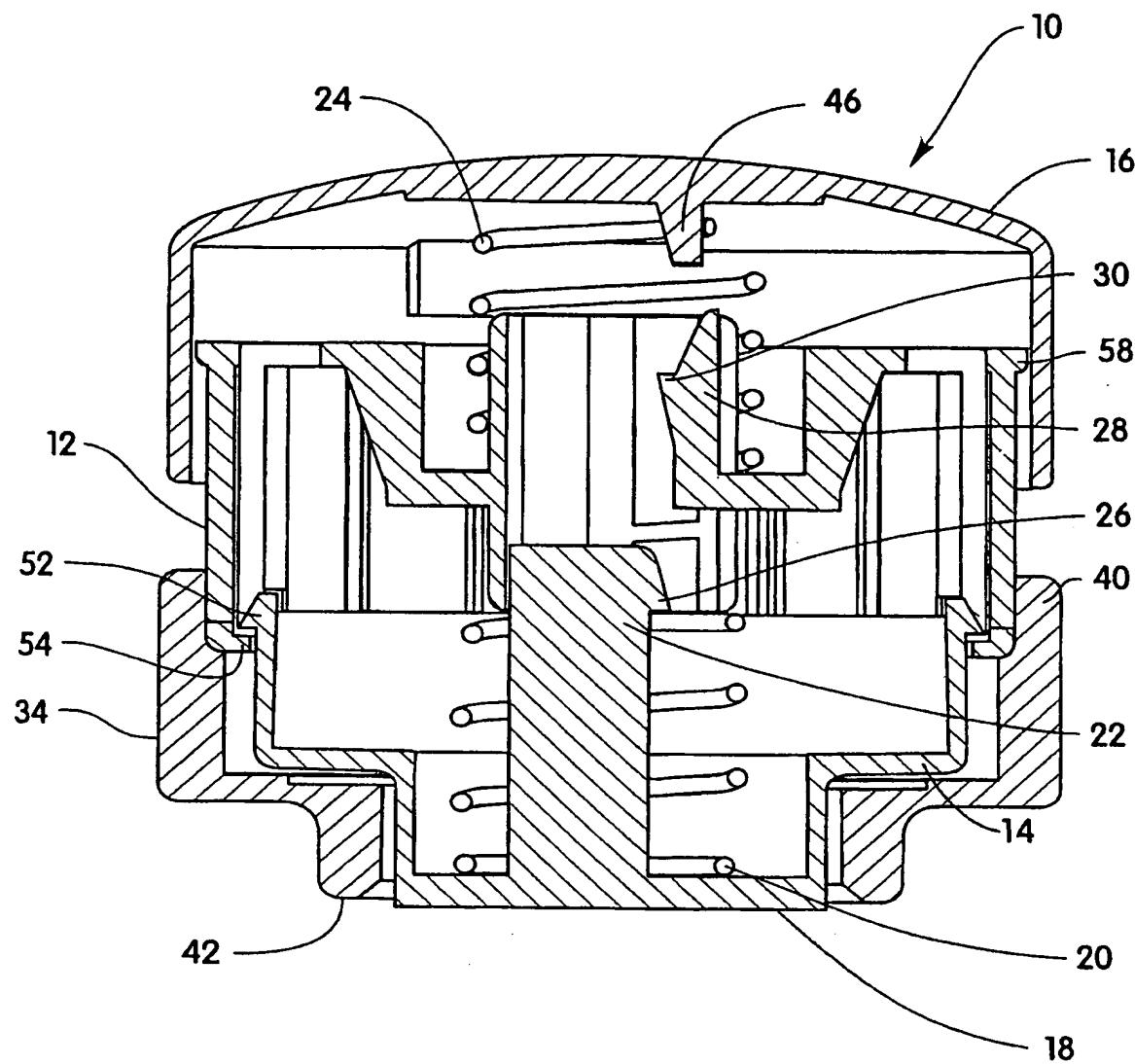


FIG. 3

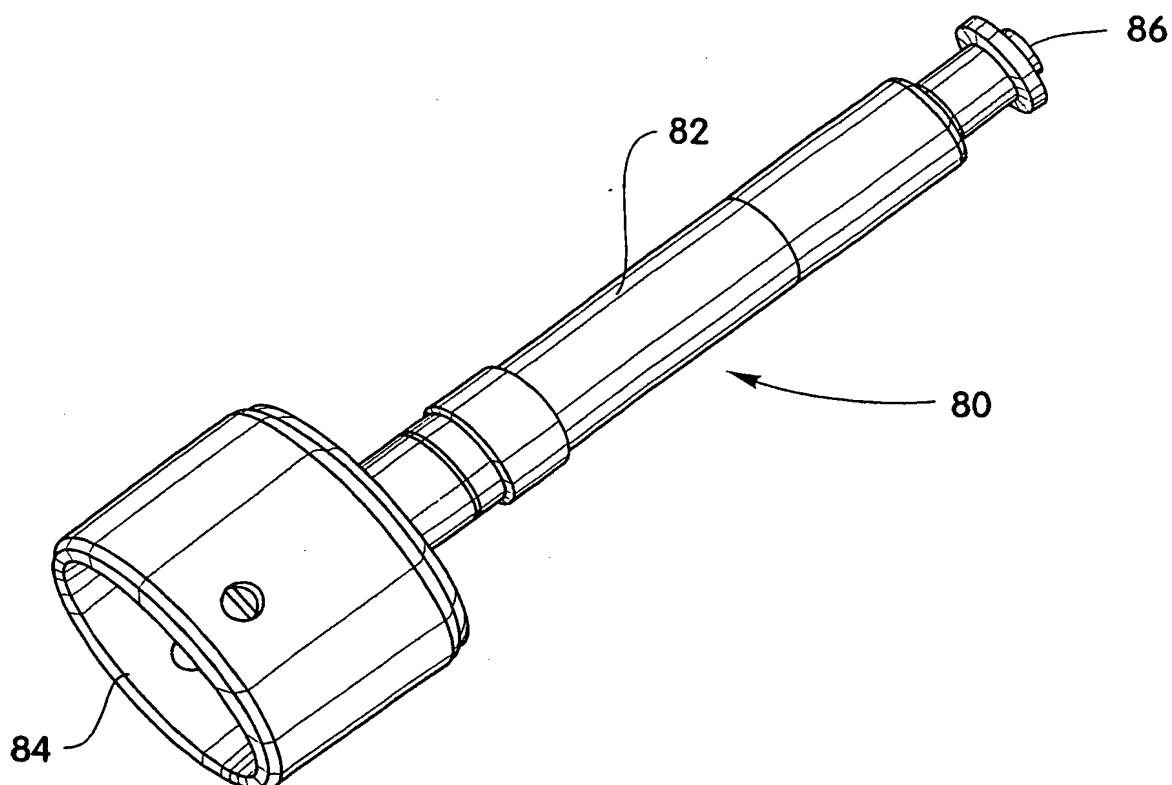


FIG. 4

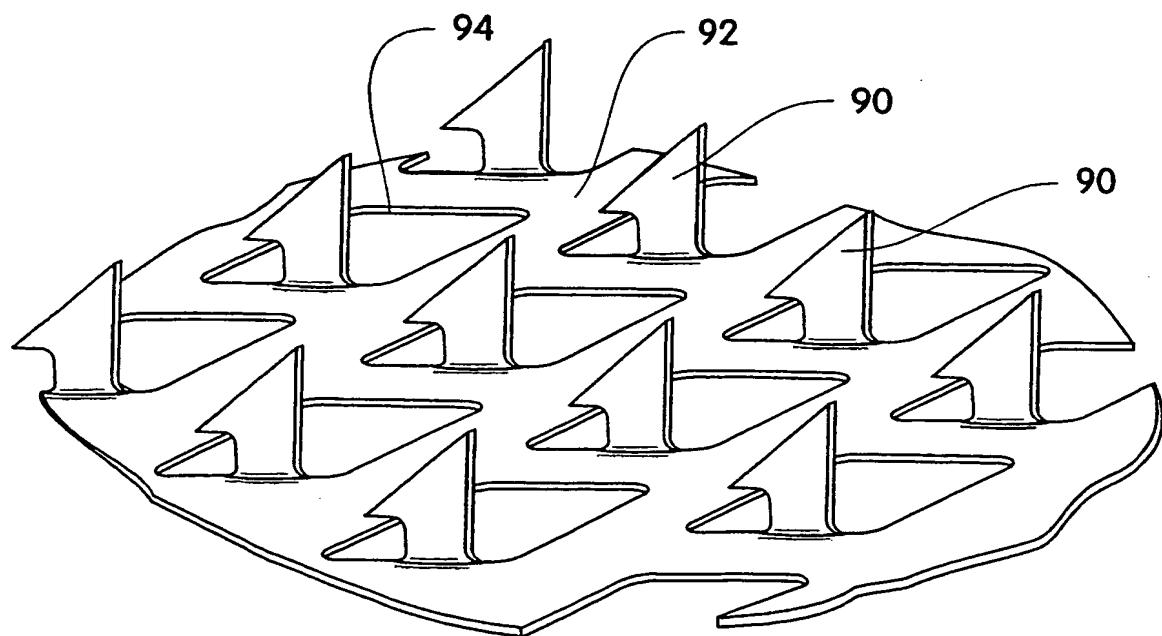


FIG. 5

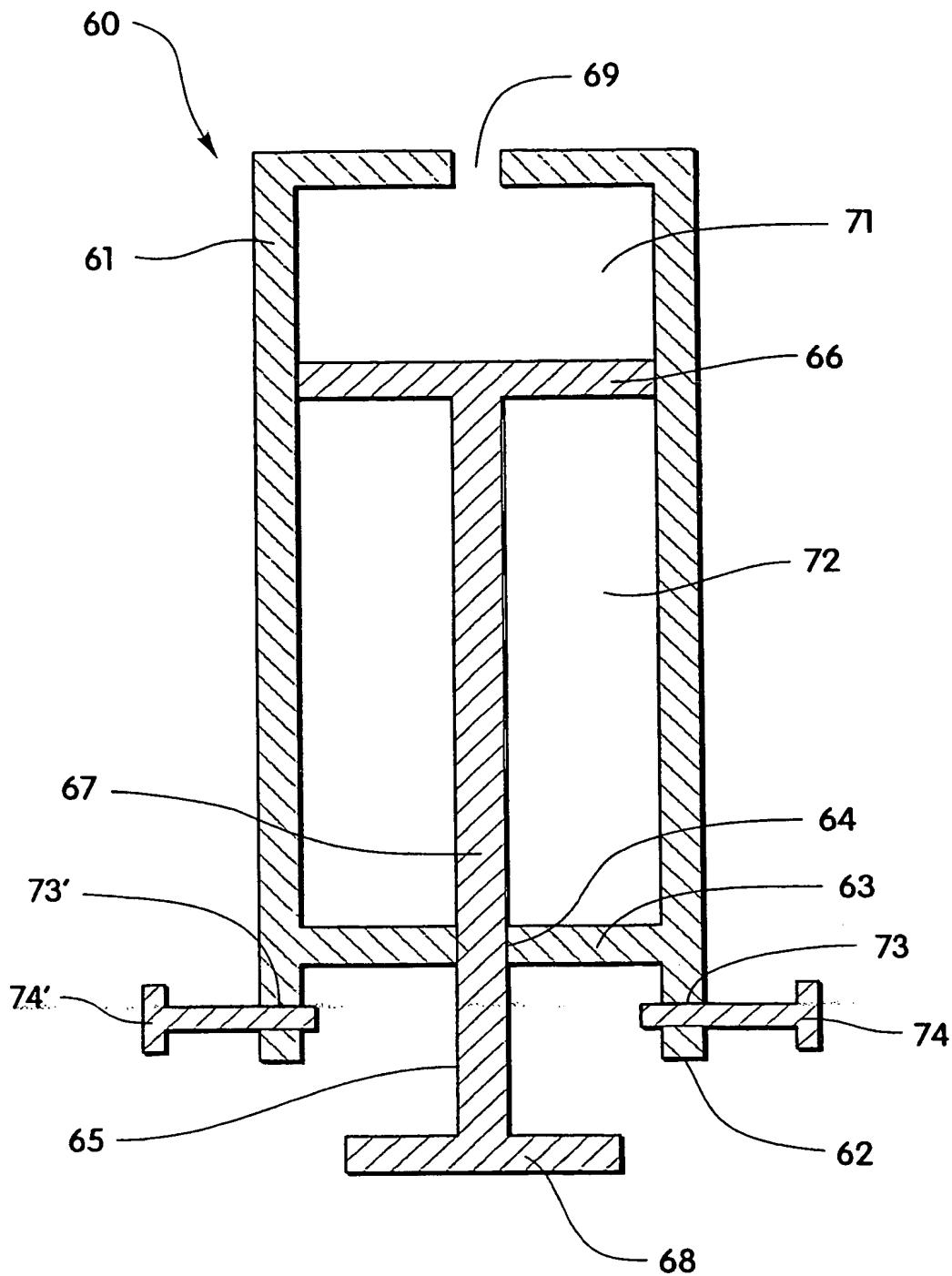


FIG. 6

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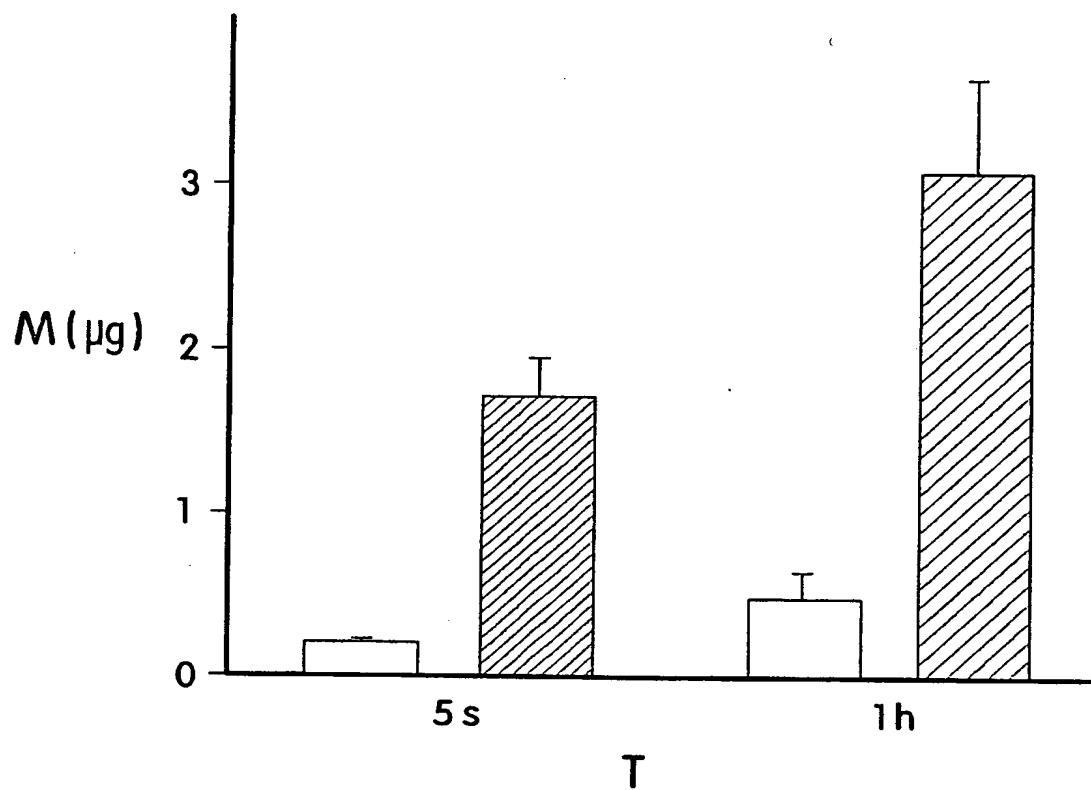


FIG. 7

## INTERNATIONAL SEARCH REPORT

tional Application No

PCT/US 01/31936

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61B17/20 A61M37/00 A61M35/00 A61N1/30

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61B A61M A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 29365 A (ALZA CORP) 17 June 1999 (1999-06-17)  page 9, line 9 - line 33; figures 5,10 ---	16,18, 20, 28-30,38
A	WO 97 48440 A (ALZA CORP) 24 December 1997 (1997-12-24) abstract; figure 2 ---	16,20, 29,38
A	US 6 048 337 A (SVEDMAN PAL) 11 April 2000 (2000-04-11)  column 20, line 1 -column 21, line 60; figures 21-24 ---	16,18, 20,29, 30,38

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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Date of the actual completion of the International search

15 February 2002

Date of mailing of the International search report

25/02/2002

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## INTERNATIONAL SEARCH REPORT

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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